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Sex differences and adverse events of antiretrovirals in people living with HIV/AIDS: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Antiretroviral therapy (ART) for HIV/AIDS is associated with adverse events (AEs). However, little is known about the differences in the risk of AEs between women and men living with HIV/AIDS. This study aims to determine (1) whether there are sex differences in the risk of AEs in people with HIV/AIDS treated with ART and (2) the prevalence of AEs to the reproductive system and bone mineral density in women.

Methods and analysis This systematic review (SR) will include randomised trials evaluating ART in people living with HIV/AIDS with at least 12 weeks of duration follow-up. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, trial registries and grey literature databases, without restriction on publication status, year of publication and language. The primary outcome will be the risk of ART discontinuation or drop-outs/withdrawals of ART due to AEs and the number of any treatment-emergent AE. The secondary outcomes are the incidence of serious clinic or laboratory (grade 3 and/or 4) treatment-emergent AEs, hospitalisation, death and AEs specific to the reproductive system and bone mineral density (osteoporosis, osteopenia and fractures) of women. Selection, data extraction and quality assessment will be performed by pairs of reviewers. Cochrane collaboration tools will be used to assess the risk of bias. If appropriate, a meta-analysis will be conducted to synthesise results. The overall quality of the evidence for each outcome will be determined by the Grades of Recommendation, Assessment, Development and Evaluation.

Ethics and dissemination The results of this SR will assist the formulation of public policies aimed at the management and monitoring of AEs of ART in people living with HIV/AIDS. A deliberative dialogue will be scheduled with the Department of Chronic Conditions and Sexually Transmitted Infections of Brazil's Ministry of Health to align the project with policymakers' interests.

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Strengths and limitations of this study

► This systematic review, in addition to studying the differences between the sexes, will scrutinise the literature to estimate the prevalence of adverse events specific to women, about which the existing literature is quite conflicting.

► This study will use the key stakeholders (eg, policymakers, opinion leader healthcare professional, community representative of patients) through deliberative dialogue, to overcome barriers to implement the evidence summarised.

► Our systematic review may have limited generalisability due to the reduced availability of data on within-study sex-by-treatment interaction effects and the possibility of aggregation bias.

► The primary studies could bring limitations to this review considering the confusion between the report of adverse events and signs and symptoms of HIV/AIDS.

INTRODUCTION

The HIV remains a major global public health problem. In 2020, 37.6 million people were living with HIV.[1] About 16% of them were unaware of being infected by the virus.[2] Most of these people are in low-income and middle-income countries.[3]

Antiretroviral therapy (ART) has now been recommended for all patients, regardless of CD4 lymphocyte count, to decrease the transmissibility of the disease and to reduce long-term complications, such as HIV-related dementia.[4] Currently, around 27.4 million people in the world use ART.[2] Since therapy must be continued indefinitely, the focus of patient management should evolve towards the identification and management of early toxicities related to pharmacological treatment.[5] Viral suppression sustained throughout life must be accompanied by individualised management

and adjustments in advance, to overcome toxicities and adverse events (AEs) in ART, both in the short and long term.[6]

In addition to HIV itself and possible AEs to ART, women need to live with hormonal changes and unique health problems.[7] Sex inequalities in response to the combination of antiretrovirals have been reported in several studies summarised in a meta-analysis.[8] ART was evaluated for at least 48 weeks, between the years 2000 and 2008, finding several significant differences related to sex, in addition to demonstrating that there was better effectiveness of ART in men than in women.

AEs to antiretrovirals have been reported with the use of all drugs and are the main reason for discontinuation, exchanges in therapy, and non-adherence to treatment.[9] Changes in the immune system, common in people with HIV, also affect female hormones, causing problems in the menstrual period, uterine fibroids, genital tract infections and early menopause.[10]

Ovarian function in women with HIV is reportedly shorter than in women uninfected by the virus, which leads to an increase in the burden of the disease as menopause impacts on the onset and progression of chronic diseases and bone mineral density (BMD).[11] Observational studies are controversial regarding the influence of ART on menstrual abnormalities. A retrospective cohort[12] was not associated with ART, while a cross-sectional study[13] showed increased abnormal menstruation in women using ART compared with treatment-naïve women (Odds Ratio (OR) 2.36, 95% CI 1.25 to 4.45). A systematic review (SR)[14] that combined six observational studies showed an increase in amenorrhoea in women with HIV, which may be associated with low BMD. The authors reinforce the need to assess the reproductive health and last menstrual period of women with the virus.

Studies suggest an increased bone mineral loss in women with HIV, but its relationship with the disease or the use of ART is uncertain. A SR[15] with one clinical trial and four cross-sectional studies showed a difference greater than 3% in BMD of the femoral neck in women using regimens containing protease inhibitors, but failed to conclude on the risk of fractures. Another review,[16] also based mainly on cross-sectional studies, points out that HIV infection reduces bone density in postmenopausal women, but that additional studies are needed to understand the mechanism of this effect and whether ART has an impact on BMD.

Brazil is considered a vanguard country in terms of healthcare policy for patients living with HIV/AIDS, especially regarding access to medication.[17] Discontinuation due to AEs, however, remains one of the central problems, even when access to the service is available.[18] Despite the general benefits of viral suppression and improved immune function due to ART far outweigh the risks associated with AEs, in general, it appears that women are more susceptible than men to develop toxicities associated with ART, and this can affect outcomes, care and treatment.[19]

Clinical studies on HIV rarely focus only on outcomes in women, with data on sex analysis often scarce and controversial.[20–22] It is worth mentioning that the long-term complications of ART can be underestimated since most clinical trials use highly specific inclusion criteria for recruiting patients and the duration of patient follow-up is relatively short.[8 23]

Understanding the occurrence of AEs associated with sex is important to assess the need to define public policies that can adapt ART to minimise the damage, improve adherence and guarantee the success of the therapy. Consequently, this could also help reduce disease transmission.[24]

In a preliminary search conducted on 16 May 2021, with the terms ('Anti-Retroviral Agents' OR 'Antiretroviral Agents' OR 'anti-HIV Agents') in the International Prospective Register of Systematic Reviews (Prospero), Open Science Framework, Cochrane Protocols; and with the title terms (Adverse AND Protocol) in the journals that publish SR protocols (eg, Systematic Reviews, BMJ Open, Plos One, Medicine) we identified 66 records of systematic review protocols, but none intended to study AEs related to sex.

This systematic review has two objectives. Objective 1 is to determine whether there are sex differences in the risk of AEs in people with HIV/AIDS treated with ART and objective 2 is to determine the prevalence of AEs to the reproductive system and BMD (osteoporosis, osteopenia and fractures) in women.

METHODS AND ANALYSIS
Study design and protocol
This SR study will be performed according to the recommendations of the Cochrane Handbook for Intervention Reviews.[25] This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols[26] (online supplemental material 1).

Patient and public involvement
We will conduct a deliberative dialogue (DD), involving relevant decision-makers, healthcare professionals, and users of the Brazilian public health system living with HIV/AIDS. We will present the results and get suggestions on implementation, monitoring, and management of AEs in women living with HIV/AIDS using the DD approach.

Eligibility criteria
The research question was structured using the Population, Intervention, Comparison and Outcomes structure.

Objective 1
Inclusion criteria
Type of studies
We will include only randomised controlled trials (RCTs) with at least 12 weeks of follow-up duration. For crossover RCTs, we will include the first period of data only.

Although observational studies may have larger samples and longer follow-up times than RCTs, providing information on rarer or longer-term AEs, non-randomised studies will be excluded due to the higher risk of bias (RoB) compared with RCTs. In an RCT, we have more monitored/controlled, standardised and reported diagnoses of AEs compared with observational studies.

Type of participants

Individuals of both sexes living with HIV/AIDS and receiving antiretroviral—regardless of age. Our study intends to analyse sex differences according to their biological definition, not the distinction between females and males by the choice of gender identity.[27]

Type of interventions

1. Any combinations of complexities and classes of ART regimens, specific ART drugs and timings of ART initiation.

Types of comparators

1. Oral placebo.
2. Any combinations of complexities and classes of ART regimens, specific ART drugs and timings of ART initiation.

Types of outcome measures

Primary outcomes

1. Risk of discontinuation or dropouts/withdrawals of ART due to AEs.
2. Risk of any AE.
3. Risk of treatment-related AEs.

Secondary outcomes

1. Risk of any serious clinic or laboratory AE (grade 3 and/or 4).
   We will extract the AEs as reported or defined by studies (serious, separate AEs grade 3, separate grade 4, grade 3, and 4). We adopted AEs grades 3 and 4 as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events.[28]
2. Risk of treatment-related serious clinic or laboratory AEs (grade 3 and/or 4).
   We will extract the AEs as reported or defined by studies (serious, separate AEs grade 3, separate grade 4, grade 3, and 4). We adopted AEs grades 3 and 4 as defined by the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events.[28]
3. Risk of osteoporosis (osteopenia, osteoporosis or any osteoporosis fractures).
4. Risk of hospitalisation
5. Risk of death due to AEs.

Objective 2
Inclusion criteria
Type of studies

We will include only RCTs with at least 12 weeks of follow-up duration. For cross-over RCTs, we will include the first period of data only. Although observational studies may have larger samples and longer follow-up times than RCTs, providing information on rarer or longer-term

AEs, non-randomised studies will be excluded due to the higher RoB compared with RCTs.

Type of participants

Women living with HIV/AIDS and receiving ART—regardless of age.

Type of interventions

1. Any combinations of complexities and classes of ART regimens, specific ART drugs, and timings of ART initiation.

Types of comparators

1. Any combinations of complexities and classes of ART regimens, specific ART drugs and timings of ART initiation.

Types of outcome measures

Prevalence of women with:

1. Delayed puberty
   It means the absence of breast development by age 12–13 years in girls.[29]
2. Amenorrhoea
   Amenorrhoea was defined as the absence of menses for more than 3 months.[14 30]
3. Other menstrual irregularities will be considered present whenever the participant reports any of the five variations from normal menstruation including changes in regularity, frequency, volume, duration and intermenstrual bleeding as defined by the International Federation of Gynecology and Obstetrics.
4. Early menopause
   Premature ovarian failure is considered when it occurs in women under the age of 40 years.[30]
5. Vasomotor symptoms of menopause (hot flushes)
   Presence of hot flushes.
   Frequency of hot flushes by severity.[31]
6. Osteopenia
   It is defined as BMD t-score −2.5 to −1 in women with 30 years or more and as BMD z-score −2 to −1 in those under 30 years.[28]
7. Osteoporosis
   It is defined as BMD t-score <−2.5 in women with 30 years or more and as BMD z-score < −2 in those under 30 years.[28]
8. Osteoporosis fractures
   Vertebral, non-vertebral, wrist, spine and hip fractures will be considered.

Objectives 1 and 2
Exclusion criteria

Studies evaluating ART regimens for HIV pre-exposure and post-exposure prophylaxis will be excluded. We will exclude studies focusing on pregnant, breastfeeding, or perinatal women; studies that examined the use of ART in the presence of co-infections, such as viral hepatitis B and C and tuberculosis; secondary or post hoc analysis; and open-label extensions. We will also exclude studies

with antiretrovirals, or ART doses no longer used in clinical practice, and with ART in the study phase, not yet used.

Search methods for identification of trials

The search strategy will use Descritores em Ciências da Saúde/Medical Subject Headings (DeCS/MeSH) descriptors and synonyms, being adapted according to each database searched (online supplemental material 2). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies (Press).[32] No limitations will be imposed on the publication status, duration of follow-up, year of publication and language (we will be using a professional translation service).

Electronic searches

A structured search for eligible primary studies will be conducted in the main electronic databases: MEDLINE via PubMed; Embase via Elsevier; Cochrane Central Register of Controlled Trials (Central); Epistemonikos; and Latin American and Caribbean Health Sciences Literature (Lilacs).

Searching other resources

A manual search will be conducted in the references of the included trials. We will adapt a specific structured search strategy for the grey literature, including dissertations databases (ProQuest Dissertations and Theses Database), records of clinical trials (Global Index Medicus of WHO—WHO; Brazilian Registry of Clinical Trials—Rebec; ClinicalTrials.gov), summaries of selected international symposium/conferences on HIV, websites of government agencies and non-governmental organisations that conduct research or implement relevant programmes.

Data collection and analysis

Selection of studies

Trial selection and data extraction will be performed based on the Cochrane Handbook for Intervention Reviews.[25] More specifically, reviewers will work in pairs and independently to assess the eligibility of titles and abstracts. A similar process will be used to track full texts. Discrepancies between the assessments will be resolved by consensus or adjudication by a third reviewer. In case of duplicate publication, we will use the article with the most complete data. Secondary publications from the same trial will also be used as online supplemental information. We will perform detailed assessments of each eligible trial to minimise the possibility of overlapping trials (ie, trials that report data from the same participants). Subsequently, two team members will independently examine the references for each full-text article to identify additional relevant studies.

Data extraction and management

A prepiloted and standardised form will be used to extract data from the included studies. The reviewers will be calibrated by extracting at least three articles, in pairs and independently, and, afterward, they will carry out consensus. This process will take place until the standardisation of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data in the different teams.

After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved (with a third author, when necessary). The data collected will be characteristics of studies (sponsorship, country, registered number, number of sites, duration of the study, timing of outcome measurement (in weeks or months); bibliometric information; information about patients (inclusion, exclusion criteria, age, ART exposure (naive vs experienced), CD4 level, numbers in each arm, drug regimen); and if the study reported AEs as specified in the section outcomes (number of participants who experienced an event) for dichotomous outcomes. We will also check the method of AE assessment: did the researchers actively monitor for AEs (low RoB), or did they simply provide spontaneous reporting of AEs that arose (high RoB)? For studies identified only in clinical trial registry websites, we will check the same data and check if they are ongoing.

When two or more papers are found for the same study, we will report it using only one ID and will extract the data of all the studies to provide the most complete report.

Assessment of methodological quality and RoB

The quality of individual studies will be assessed using Cochrane's RoB Tool version 2.0 for randomised trials on bias arising from the randomisation process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. The reviewers will independently assign 'definitely yes', 'probably yes', 'probably not', 'definitely not' or 'not informed' for each of the domains, classifying, according to the answers, as 'low RoB', 'some concern about the RoB' or 'high RoB'. Reviewers will resolve disagreements through discussion, and a third person will judge unresolved disagreements. Publication bias will be assessed using the funnel graph[33] for each outcome.

Statistical analysis

Objective 1

The statistical approach to summarise trial results will depend vastly on the type of available data. Differences between sexes in the risk of an event after treatment with antiretrovirals can be considered covariate-by-treatment interactions. Hence, we will attempt to employ statistical techniques that explicitly disentangle within-trial interactions effects from between-trial interaction effects, thereby minimising the risk of ecological bias.[34]

We anticipate that some trials may report information sufficient to reconstruct individual-participant data (IPD) (eg, the number of events by treatment group stratified by sex). In contrast, other trials may report information

adequate to calculate only the OR of the event and the proportion of women in each arm (ie, aggregate data only). Thus, our primary analysis model will be based on an adaption of the model by Saramago *et al*.[35] Specifically, we will use a Bayesian IPD-AD pair-wise random-effects model that separates the within-trial interaction effects from between-trial interaction effects.

However, if only aggregate data is available (eg, OR estimates and proportion of female by treatment group), we will perform a 'daft' approach, combining across-trial interactions alone.[34] More specifically, we will conduct a Bayesian random-effects meta-regression to assess the association between the log-odds of the event and the proportion of women in the trial. We will graphically display these results using bubble plots and prediction lines with 95% credible intervals.

If only aggregate data is available, but it is possible to estimate the OR by sex separately, we will perform the 'deft' approach, combining within-trial interactions only. This approach eliminates the risk of ecological bias seen in the daft approach.[34] The log ratio of ORs will be used as a metric, and the summary estimate will be obtained by a Bayesian random-effects model.[36]

All primary analyses will employ uninformative priors. However, for the between-trial variances, we will use informative prior distributions in sensitivity analyses.[37] We will estimate the between-trial heterogeneity from the median between-trial variance, $\tau 2$, observed in the posterior distribution. A τ^2 of up to 0.04 was prespecified to denote low heterogeneity, 0.16 to denote moderate, and 0.36 to denote high statistical heterogeneity among trial estimates.[38]

Ninety-five per cent credible intervals (95% CrIs) will be calculated from the 2.5 and 97.5 percentiles of the posterior distributions. Bayesian models will be implemented in the BUGS language, and estimates will be obtained via Markov chain Monte Carlo methods (Gibbs sampling). Convergence will be checked graphically by running three chains and using the Gelman-Rubin statistic. An R statistic >1.1 will be considered evidence of non-convergence.[39] The burning-in period will have 100 000 simulations, and three different chains with 166 667 simulations each will be used (500 000 simulations in total). Starting values were manually selected to guarantee very different random draws for the three chains. Results were summarised using posterior medians with 95% CrIs. The autocorrelation and density of the estimates were checked graphically. Funnel plot asymmetry will be examined by contour-enhanced plots using frequentist estimates of log-OR on the horizontal axis and their corresponding SE estimates on the vertical axis. We will also investigate funnel plot asymmetry with Habord's test. For the latter, a p<0.10 will be considered statistically significant.

For all analyses, we will use Stata V.16 and MultiBUGS V.2.0 (Cambridge, UK).

Objective 2

We will meta-analyse proportions using a random-effects Bayesian model. Specifically, the model uses the binomial likelihood and the logit transformation of the proportions. The proportions are considered a random variable, and the mean of the logit proportions is assumed to follow a normal distribution.[40] We will use a non-informative prior for the mean of the logit-transformed study-specific proportions and the between-study variance. The burning-in period will have 50 000 simulations, and three different chains with 50 000 simulations each will be used (150 000 simulations in total). Starting values were manually selected to guarantee very different random draws for the three chains. Results were summarised using posterior medians with 95% CrIs. All model diagnostics will be performed as described above.

Subgroup analysis or sensitivity analysis

When appropriate, subgroup analysis will be employed. The subgroup that will be used includes age groups (<18 years vs 18–60 years vs >60 years); level of economic development of the study setting (low or lower-middle-income country vs middle or high-income country, as defined by the World Bank[41]); immunological status (CD4 <250 *vs* CD4 ≥250 cells/μL); time of follow-up (≤24 weeks vs 25 to 48 weeks *vs* ≥48 weeks); industry-independent funding (no vs yes); Intention-to-treat (ITT) analysis of AEs (no vs yes); attribution of AEs to drugs (no vs yes); combined vs single ART; RoB (high vs moderated and low; blinded vs open-label; adequate allocation concealment vs unclear allocation concealment).

Assessment of the certainty of the evidence and the strength of the recommendation

After the results are grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[42] The main results of the review will be presented in outcome tables (Summary of Findings (SoF)), as recommended by The Cochrane Collaboration.[43] The SoF table includes a general classification of the evidence related to each of the main outcomes, using the GRADE approach.[44] This table will be built with the aid of the GRADEpro software program.

The use of the GRADE allows evaluating the certainty of the evidence for each result considering the methodological quality, the objectivity of the evidence, the heterogeneity, the precision of the effect estimates and the risk of publication bias.[43] If the analysis of an outcome is not possible, for example, due to the lack of data, we will present the reasons for this in the SoF table as a footnote.

ETHICS AND DISSEMINATION

We plan on sharing our results through publication in scientific journals of high impact, peer-reviewed, and presenting it at national and international conferences.

We hope that the results will serve to assist in the formulation of public policies aimed at guiding professionals on the management and monitoring of the AEs of ART in people living with HIV/AIDS. For this purpose, meetings are scheduled with the Department of Chronic Conditions and Sexually Transmitted Infections of Brazil's Ministry of Health during the project, seeking to align it with the interests of policy-makers.

We will also present the results and discuss the implementation, monitoring, and management of AEs in people living with HIV/AIDS in a DD with stakeholders, policymakers, and other researchers. Considering that the results of the DD can make adjustments in the recommendations of the SR, the stakeholders have to disclaim their potential conflicts of interest. For this reason, this protocol will be submitted for approval to the ethics committee before the conduction of the DD.

DISCUSSION

The results of this SR could highlight important findings to decision-making, considering the management of AEs in the different age ranges of women.

Our future results could impact public policies for people living with HIV/AIDS by offering evidence that can highlight challenges and areas of improvement, with a special view over the diversity of people and their contexts. However, there are potential limitations.

The primary studies could bring limitations to this review considering the confusion between the report of AEs and signs and symptoms of HIV/AIDS; some trials do not report the time of initiation of ART and do not separate the outcomes by sex. To overcome this limitation, we will extract the information of all trials that report the time of initiation of ART and if possible, we will meta-analyse this result.

Antiretroviral drugs also are usually given in combination, being difficult to ascertain which agent causes the AE, this could be another potential limitation of this SR.

This study did not include real-world studies that reported adverse drug reactions in patients receiving antiretrovirals because we consider that RCTs provide a more accurate diagnosis of AEs as they can be better monitored/controlled, standardised and reported compared with real-world studies.

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REFERENCES

1 HIV/AIDS fact sheet Geneva: World Health Organization, 2019. Available: https://www.who.int/news-room/fact-sheets/detail/hiv-aids
2 UNAIDS. Global HIV & AIDS statistics — 2020 fact sheet, 2020. Available: https://www.unaids.org/en/resources/fact-sheet
3 UNAIDS. Ending AIDS progress towards the 90-90-90 targets, 2017. Available: https://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf
4 Brazil. *Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em Adultos*. Brasília: Ministério da Saúde, 2018.
5 World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. Geneva, 2016. http://www.who.int/hiv/pub/arv/arv-2016/en
6 Brazil. *Cuidado integral s pessoas que vivem com HIV pela Atenção Básica: manual para a equipe multiprofissional*. Brasília: Ministério da Saúde, 2017.
7 Scully EP. Sex differences in HIV infection. *Curr HIV/AIDS Rep* 2018;15:136–46.
8 Soon GG, Min M, Struble KA, *et al*. Meta-analysis of gender differences in efficacy outcomes for HIV-positive subjects in

randomized controlled clinical trials of antiretroviral therapy (2000-2008). *AIDS Patient Care STDS* 2012;26:444–53.

9 Gesesew HA, Ward P, Hajito KW, *et al*. Discontinuation from antiretroviral therapy: a continuing challenge among adults in HIV care in Ethiopia: a systematic review and meta-analysis. *PLoS One* 2017;12:e0169651.

10 Cejtin HE. Gynecologic issues in the HIV-infected woman. *Infect Dis Clin North Am* 2008;22:709–39.

11 Imai K, Sutton MY, Mdodo R, *et al*. HIV and menopause: a systematic review of the effects of HIV infection on age at menopause and the effects of menopause on response to antiretroviral therapy. *Obstet Gynecol Int* 2013;2013:1–11.

12 Massad LS, Evans CT, Minkoff H, *et al*. Effects of HIV infection and its treatment on self-reported menstrual abnormalities in women. *J Womens Health* 2006;15:591–8.

13 Valiaveettil C, Loutfy M, Kennedy VL, *et al*. High prevalence of abnormal menstruation among women living with HIV in Canada. *PLoS One* 2019;14:e0226992.

14 King EM, Albert AY, Murray MCM. HIV and amenorrhea: a meta-analysis. *AIDS* 2019;33:483–91.

15 Carvalho EHde, Gelenske T, Bandeira F, *et al*. Bone mineral density in HIV-infected women taking antiretroviral therapy: a systematic review. *Arq Bras Endocrinol Metabol* 2010;54:133–42.

16 Cezarino PYA, Simões RDS, Baracat EC, *et al*. Are women living with HIV prone to osteoporosis in postmenopause? A systematic review. *Rev Assoc Med Bras* 2018;64:469–73.

17 Brazil. "O Brasil tem um dos melhores programas de HIV/aids do mundo", diz Drauzio Varella, 2018. Available: http://www.aids.gov.br/pt-br/noticias/o-brasil-tem-um-dos-melhores-programas-de-hivaids-do-mundo-diz-drauzio-varella

18 Li H, Marley G, Ma W, *et al*. The role of ARV associated adverse drug reactions in influencing adherence among HIV-infected individuals: a systematic review and qualitative Meta-Synthesis. *AIDS Behav* 2017;21:341–51.

19 Geretti AM, Loutfy M, D'Arminio Monforte A, *et al*. Out of focus: tailoring the cascade of care to the needs of women living with HIV. *HIV Med* 2017;18 Suppl 2:3–17.

20 Loutfy MR, Sherr L, Sonnenberg-Schwan U, *et al*. Caring for women living with HIV: gaps in the evidence. *J Int AIDS Soc* 2013;16:18509.

21 Rosin C, Elzi L, Thurnheer C, *et al*. Gender inequalities in the response to combination antiretroviral therapy over time: the Swiss HIV cohort study. *HIV Med* 2015;16:319–25.

22 Loutfy MR, Walmsley SL, Klein MB, *et al*. Factors affecting antiretroviral pharmacokinetics in HIV-infected women with virologic suppression on combination antiretroviral therapy: a cross-sectional study. *BMC Infect Dis* 2013;13:256.

23 Curno MJ, Rossi S, Hodges-Mameletzis I, *et al*. A systematic review of the inclusion (or exclusion) of women in HIV research: from clinical studies of antiretrovirals and vaccines to cure strategies. *J Acquir Immune Defic Syndr* 2016;71:181–8.

24 Hewitt RG PN, Gugino L. *The role of gender in HIV progression*. . Spring, 2001: 14. 13–16.

25 Cochrane. Cochrane Handbook for systematic reviews of interventions. Available: https://training.cochrane.org/handbook

26 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

27 et alDoull M, Shea B, Puil L. Addressing Sex/Gender in systematic reviews: cochrane HIV/AIDS group Briefing note. version 2014-01, 2021. Available: http://equity.cochrane.org/sex-and-gender-analysis

28 U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, AIDS Do. Table for grading the severity of adult and pediatric adverse events, corrected version 2.1, 2017. Available: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

29 Crowley WF, Pitteloud N. Approach to the patient with delayed puberty UpToDate, 2020. Available: https://www.uptodate.com/contents/approach-to-the-patient-with-delayed-puberty

30 Munro MG, Critchley HOD, Fraser GS. *Abnormal uterine bleeding in reproductive-age patients: FIGO system 1 terminology and symptoms and system 2 PALM-COEIN etiology classification: UpToDate*, 2021.

31 Maclennan AH, Broadbent JL, Lester S, *et al*. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2004;2004:Cd002978.

32 McGowan J, Sampson M, Salzwedel DM, *et al*. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;75:40–6.

33 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.

34 Fisher DJ, Carpenter JR, Morris TP, *et al*. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017;356:j573.

35 Saramago P, Sutton AJ, Cooper NJ, *et al*. Mixed treatment comparisons using aggregate and individual participant level data. *Stat Med* 2012;31:3516–36.

36 Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. *Stat Med* 2002;21:1601–23.

37 Turner RM, Davey J, Clarke MJ, *et al*. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane database of systematic reviews. *Int J Epidemiol* 2012;41:818–27.

38 da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J* 2014;35:3336–45.

39 Kanters S, Karim ME, Thorlund K, *et al*. When does the use of individual patient data in network meta-analysis make a difference? A simulation study. *BMC Med Res Methodol* 2021;21:21.

40 Wong WL, Su X, Li X, *et al*. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health* 2014;2:e106–16.

41 World Bank. Country and lending groups, 2021. Available: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519

42 Guyatt GH, Oxman AD, Schünemann HJ, *et al*. GRADE guidelines: a new series of articles in the Journal of clinical epidemiology. *J Clin Epidemiol* 2011;64:380–2.

43 Grade Handbook, 2013. Available: https://gdt.gradepro.org/app/handbook/handbook.html

44 Balshem H, Helfand M, Schünemann HJ, *et al*. Grade guidelines: 3. rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.